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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/019,375	03/05/2002	Lawrence C. Smith	1051-1-020	6403

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EXAMINER	
CROUCH, DEBORAH	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 06/23/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/019,375	SMITH ET AL.	
	Examiner	Art Unit	
	Deborah Crouch, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-38 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-38 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 05 March 2002 is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Claims 1-38 are pending and subject to the examination below.

Claims 8, 16 and 34 are objected to with regards to the term "cytosqueletal." This is not an English term. The Examiner believes that applicant intends the term to be "cytoskeletal," which is the term adopted for examination purposes. The specification also contains this term (specification, page 6, line 22, as example). Applicant should correct the claims and the specification in response to this office action.

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 25-27 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The PTO does allow claims to or than encompass humans. Claims 25, drawn to a transgenic embryo, a transgenic fetus and a transgenic offspring, include humans in their scope. Applicant should limit their claims to "nonhuman."

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-24 and 28-38 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the method of preparing a reconstructed nonhuman mammalian oocyte, a method of reconstituting a nonhuman mammalian embryo, methods for production of a transgenic nonhuman mammalian embryo and methods of cloning a nonhuman mammal, where the donor cell, the oocyte and the surrogate mother are all of the same species, does not reasonably provide enablement for cross-species nuclear transfer. The specification does not enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

At the time of filing, techniques of nuclear transfer were regarded by the art as unpredictable. The claims are not enabled because at the time of filing the, art taught that it was unpredictable to clone successfully for the breath of the claims which encompasses all mammals, reptiles, fish, birds and amphibians. Even for mammals, the art taught that their cloning was unpredictable. In regard to this, Westhusin, states that one of the major factors influencing a successful cloning outcome is species of target animal. Westhusin goes on to state that while the basic methodology for nuclear transfer may be similar, the specific materials and methods do not automatically apply across all species. Westhusin outlines six factors which contribute to successful cloning: 1) acquisition of mature ova, 2) removing the chromosomes contained within the ova, 3) transfer of cell nuclei obtained from the animal to be cloned into enucleated ova, 4) activation of the newly formed embryo, 5) embryo culture in vitro, and 6) transfer of the cloned embryo into a surrogate mother. There is no guidance in the specification or the art on, for example, activation of enucleated Drosophila eggs or lobster eggs, much less how to enucleate them for successful nuclear transfer. Westhusin further states that each of these steps will vary slightly between species, but that, more importantly, the efficiency of each step varies among species, ultimately affecting the ease of which a particular animal can be cloned (Westhusin, page 36-37, bridg. parag.). This analysis is supported by Polejaeva that states, in regard to the inefficiency of cloning, that several factors affect the inefficiency: laboratory to laboratory variation, oocyte source and quality, methods of embryo culture, donor cell type, possible loss of somatic imprinting in the nuclei of the reconstructed embryo, failure to reprogram the transplanted nucleus adequately, and failure of artificial methods of activation to emulate reproducibly those crucial membrane-mediated events that accompany fertilization (Polejaeva, page 1,

parag. 2). Thus nuclear transfer, at the time of filing was not routine, but requires extensive experimentation without a predictable degree of success. Pennisi and several scientists working in the area of mammalian cloning point to a lack of general and reproducible success emphasize this. Robert Wall of the USDA is quoted as stating that despite years of effort, "[w]e're in the same bind that we've always been in. A majority of [would be clones] do not make it to term." (Pennisi, page 1722, col. 1, parag. 2, lines 9-14). Pennisi and Vogel state, "even when an embryo does successfully implant in the womb, pregnancies often end in miscarriages" (Pennisi, page 1722, col. 1, parag. 3, lines 16-18). Attempts to clone pigs using techniques successful in sheep were not successful; indicating that cross-species application of methodology is unpredictable (Pennisi, page 1725, col. 1-2, bridg. parag.). The case with rabbits indicates that obtaining an embryo by nuclear transfer does not translate into a cloned rabbit. While many cloned rabbit embryos can be made, they abort upon transfer to surrogate mothers, and in 2000, there had not been any successes in cloning rabbits (Pennisi, page 1725, col. 2, parag. 3). With primates, two cloned monkeys were produced, but there have been no subsequent successes in primate cloning (Pennisi, page 1726, col. 2, line 6 to col. 3, line 3). With regard to cats, one cloned cat has been produced, but given the difficulty in the art to produce a cloned cat and the lack of producibility as stated above, the cloning of cats is unpredictable. Two attempts to implant cat eggs or reconstructed embryos failed, providing for an unpredictable outcome for cat cloning (Pennisi, page 1726, col. 2, parag. 3, lines 4-5). Others have reported establishing pregnancies but no report of a cloned cat being born (Pennisi, page 1726, col. 2, parag. 3, lines 5-9 and 11-12). As the authors state, establishing pregnancies is only part of the problem and is not a guarantee of a cloned mammal being produced (Pennisi, page 1726, col. 2, lines 9-11). Thus, at the time of filing, there appears to be such unpredictability that only the cloning of sheep, cows, and rodents were predictable. Particularly noteworthy,

given that applicant's claims encompass the cloning of humans, is a report that the cloning of monkeys, a primate, by nuclear transfer had been successful when embryonic cells were the nuclear donor, not when somatic cells were used as nuclear donor (Mitalipov, abstract). Mitalipov further states, clearly, that somatic cell cloning, as is part of the present methods, has not been accomplished in primates (Mitalipov, page 1367, col. 2, parag, 3, lines 1-3). Simerly, states that in rhesus monkey NT units, DNA and microtubule imaging showed disarrayed mitotic spindles with misaligned chromosomes, which resulted in unequal chromosome segregation and aneuploid embryos (Simerly, page 297, col. 2, parag. 1, lines 5-11). Thus, mammalian cloning, and by extension all nonhuman cloning, is unpredictable for all the reasons cited above.

It was known at the time of filing, that cross-species nuclear transfer was unpredictable in both embryo and term development. Meirelles demonstrate that methods of nuclear transfer where the nuclear material of *Bos indicus* is inserted into the oocyte of *Bos taurus* produces calves comprising the nuclear material of *Bos indicus* and the mitochondria of *Bos taurus*. Meirelles *et al*. teach that previous attempts to use the *Bos* oocyte as hosts for nuclear transfer from unrelated species allowed development to the blastocyst stage, however conclude that incompatibility among the nuclear and mitochondrial genetic systems is responsible for the early arrest. Meirelles *et al*. also point to similar failures using *Mus caroli* and *Mus musculus* citing Dominko *et al*. discussed in length in the previous office action. Meirelles *et al*. conclude that in light of their results and the failures of the prior art, that nuclear transfer across subspecies barriers is possible. (see Meirelles, pp. 351-355). Applicant's claims encompass nuclear transfer (cloning) when the nucleus is of one species and the oocyte is of another species. This clearly lacks predictability given the teachings of Meirelles. Further, in the production of sheep goat chimeras, there were biases towards chimeras whose genotype and phenotype was most

like that of the recipient, and that the successful production of chimeras resided in the neutralization of incompatibility between the chimeric embryo (Fehilly et al (1985), page 221, parag. 1). This is also an unpredictable feature of the claimed invention as an embryo of one species implanted into a surrogate mother of another species is unlikely to develop given the teaching of Fehilly. The specification does not provide guidance on producing cross-species embryo or animals, nor how to overcome the unpredictable nature of cross-species cloning.

The specification is deficient in providing any guidance on overcoming these art recognized unpredictabilities. There is no discussion or working examples, which describe cloning methods that permit the cloning of the diverse nonhumans encompassed by the claims. Further, there is no guidance or working example for cross-species nuclear transfer, also encompassed by the claims.

Therefore, in view of the reasons presented above, the claimed invention is unpredictable because at the time of filing the skilled artisan would need to engage in an undue amount of experimentation without a predictable degree of success to implement the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claim 19 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 19 does not further limit claim 10. Claim 10 is to a method of making an embryo. Claims 19 states that the embryo develops into a nonhuman mammal, which takes

the claim past the production of an embryo. Applicant should enter a separate claim or claims drawn to a method of producing a nonhuman mammal.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-18 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Bordignon et al (1998) Molec. Reprod. Devel. 49, 29-36.

Bordignon teaches methods of preparing a reconstituted nonhuman oocyte and methods of reconstituting a nonhuman embryo by activating an MII oocyte by ethanol treatment (page 30, col. 2, parag. 1, lines 7-11), permitting the oocyte to mature to telophase II where there is at extrusion of the second polar body (pages 31-32, bridg. sent.), enucleating the telophase II oocyte in the presence of cytochalasin B by removing the nucleus a portion of the surrounding cytoplasm using a micropipette (microsurgery) (page 32, col. 1, lines 2-5), electro-fusing a blastomere isolated from an IVF 5.5 day blastocyst to introduce a germinal cell nucleus into the enucleated oocyte (page 31, col. 1, parag. 2, lines 15-21 and page 32, col. 1, lines 5-9), and culturing in vitro the reconstructed embryo into a blastocyst (page 32, col. 1, lines 9-14). The blastomeres are inherently in G1, S, G2 or M stage of division as blastomeres are actively dividing, and G1, S, G2 or M are stages representative of actively dividing cells. IVF inherently causes the blastomere to be cultured. Thus, Bordignon clearly anticipates the claimed invention.

Claims 25-27 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Cibelli et al (1998) Theriogenology 49, page 236.

Cibelli teaches transgenic bovines embryos and transgenic bovines, and inherent transgenic bovine fetus (page 236, parag. 2). While Cibelli discloses the production of the embryos and bovines, and inherently the fetus by somatic cell nuclear transfer, where fetal fibroblasts were transfected with a gene for neomycin resistance, the transfected cells fused to mature bovine oocytes, the resulting reconstituted bovine embryos were grown to the blastocyst stage and transferred to reciepient cows, with live transgenic calf births resulting (page 236, parag. 2), there is no evidence that the method of making the claimed products alters them such that they can be distinguished from the bovine embryos, fetuses and bovines of Cibelli.

Where, as here, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product (*In re Ludtke*). Whether the rejection is based on "inherency" under 35 USC 102, on "prima facie obviousness" under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products. *In re Best, Bolton, and Shaw*, 195 USPQ 430, 433 (CCPA 1977) citing *In re Brown*, 59 CCPA 1036, 459 F.2d 531, 173 USPQ 685 (1972). The PTO does not have the means to determine if the presently claimed transgenic embryo, transgenic fetus or transgenic offspring are identical to those disclosed in Cibelli.

> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.
>
> The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting

> directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 1-38 are rejected under 35 U.S.C. 102(e) as being clearly anticipated by U.S. Patent 6,580,017 B1 issued June 17, 2003 (Echelard).

Echelard teaches methods for the production of reconstructed goat oocytes, reconstituted goat embryos, methods fro the production of transgenic goat embryos, a method of cloning a goat, methods for producing transgenic goat embryos, and methods of cloning a goat comprising activating an oocyte by incubation in 7% ethanol (col. 19, lines 15-19), incubating the activated oocyte to telophase II and then further incubating the oocyte in the presence of cytochalasin B, enucleating the activated, telophase II oocyte by aspiration (col. 19, lines 14-25), transferring a cultured goat fetal fibroblast which contains a DNA sequence encoding antithrombin III (col. 16, lines 19-25 and lines 42-44) into the perivitiline space of the enucleated oocyte (col. 19, lines 35-40), fusing the reconstructed oocyte by electrofusion (col. 19, lines 48-52), culturing the reconstituted oocyte to produce an transgenic embryo (col. 21, lines 22-24), which is then transferred to a surrogate mother goat to produce a transgenic goat offspring (col. 21, lines 25-27 and col. 22, line 52). The fibroblast donor cells were inherently in on of G0, G1, S, G2 or M as these are all the stages of the cell cycle. Further, Echelard teaches transgenic goat embryos, fetuses and offspring. Thus, Echelard clearly anticipates the claimed invention.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 19-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bordignon in view of Cibelli et al (1998) Theriogenology 49, page 236.

Bordignon et al (1998) Molec. Reprod. Devel. 49, 29-36.

Bordignon teaches methods of preparing a reconstituted bovine oocyte and methods of reconstituting a bovine embryo by activating an MII oocyte by ethanol treatment (page 30, col. 2, parag. 1, lines 7-11), permitting the oocyte to mature to telophase II where there is at extrusion of the second polar body (pages 31-32, bridg. sent.), enucleating the telophase II oocyte in the presence of cytochalasin B by removing the nucleus a portion of the surrounding cytoplasm using a micropipette (microsurgery) (page 32, col. 1, lines 2-5), electro-fusing a blastomere isolated from an IVF 5.5 day blastocyst to introduce a germinal cell nucleus into the enucleated oocyte (page 31, col. 1, parag. 2, lines 15-21 and page 32, col. 1, lines 5-9), and culturing in vitro the reconstructed embryo into a blastocyst (page 32, col. 1, lines 9-14). The blastomeres are inherently in G1, S, G2 or M stage of division as blastomeres are actively dividing, and G1, S, G2 or M are stages representative of actively dividing cells. IVF inherently causes the blastomere to be cultured.

Cibelli teaches the production of transgenic bovines by somatic cell nuclear transfer, where fetal fibroblasts were transfected with a gene for neomycin resistance, the transfected cells fused to mature bovine oocytes, the resulting reconstituted bovine embryos were grown to the blastocyst stage and transferred to reciepient cows, with live transgenic calf births resulting (page 236, parag. 2).

Motivation for using enucleated telophase oocytes is given by Bordignon in stating that when compared to the use of metaphase oocytes, telophase oocytes permitted the formation of blastocyst-stage embryos that had a larger number of cells (page 35, col. 1, parag. 1, lines 1-5). Motivation for producing transgenic bovines by nuclear transfer comes

from a need in the art to produce genetically identical individuals for husbandry purposes such quality and quantity milk producers.

Thus at the time of filing, it would have been obvious to the ordinary artisan to produced transgenic bovines by nuclear transfer given the teachings of Bordignon that bovine blastocyst could be produced using telophase oocytes in view of Cibelli teaching the production of transgenic bovines by somatic cell nuclear transfer. The cited prior art provides the requisite teaching, suggestion and motivation to reach the invention of the claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deborah Crouch, Ph.D. whose telephone number is 571-272-0727. The examiner can normally be reached on M-Th, 8:30 AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on 571-272-0408. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Deborah Crouch

Deborah Crouch, Ph.D.
Primary Examiner
Art Unit 1632

June 19, 2004